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The Fourteenth Report of the

NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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The Fourteenth Report of the

NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Heart, Lung,
and Blood Institute
Bethesda, Maryland 20892

The President
The White House
Washington, D.C.

Dear Mr. President:

We are pleased to submit to you our fourteenth report on the progress of the National Heart, Lung, and Blood Institute's program to control and prevent diseases of the heart, lung, and blood, as well as to ensure an adequate and a safe supply of blood resources. In submitting this report, we wish to take this opportunity to thank you, the Congress, and the Institute for the privilege of serving the people of this country.

Respectfully,

The National Heart, Lung,
and Blood Advisory Council

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INTRODUCTION

People. That's why the National Heart, Lung, and Blood Institute exists—for the people of our Nation. The Institute's mandate is to improve our health by supporting and conducting research and training into the causes, the diagnosis, the treatment, the cure, and ultimately the prevention of diseases of the heart, lungs, and blood. The Institute also strives to ensure a safe and an adequate supply of blood resources.

In this report, therefore, the National Heart, Lung, and Blood Advisory Council has focused on the impact of clinical advances and biomedical research supported by the Institute on the lives of individuals. The first three chapters— Heart and Vascular Diseases, Lung Diseases, and Blood Diseases and Resources—begin with a discussion of several individuals whose lives have been or, we hope, will some day be made better as a result of Institute-supported research. These discussions are followed by highlights of scientific progress in several other areas.

The final chapter of the report discusses Institute goals, priorities, and resource needs in the immediate future. The topics include, among others: clinical trials, which are large-scale studies designed to test the effectiveness and safety of preventive and therapeutic regimens before they are introduced into practice; the Institute's efforts to enhance minority representation in the biomedical research community; the Council's concern for the plight of newly trained investigators with great potential who have not been successful in getting research funds; and a recommended budget for the Institute for fiscal years 1988 through 1992.

Today, the biomedical research community seems poised to make a great many significant advances. The investigators are highly motivated and well trained. They have access to sophisticated research facilities and equipment. Considerable progress has already been accomplished in several areas; for example, death rates from coronary disease have declined about 34 percent from 1970 to 1984. There is, however, a major problem—grossly inadequate research funds. Because of insufficient funding, too many gifted basic science and clinical investigators are being turned away. Because of this situation, too many promising ideas remain untried. Too many potential opportunities to improve the health of the people of the United States and the world are being missed. The biomedical research budget must be less restrictive. Our future depends on it.

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Introduction

More than 1.25 million people in the United States had a heart attack in 1985—over 3,400 each day. About 550,000 of these heart attack sufferers died (350,000 before they reached the hospital) making heart attack the greatest single cause of death in the United States and a health problem of gigantic human and social proportions.

In addition to the cost in human life and quality of life, the economic cost of cardiovascular disease was estimated by the American Heart Association to be $72.1 billion in 1985. This figure includes physician and nursing services, hospital and nursing home services, medications, and lost output because of disability. Most of the cost, $43.7 billion, was for hospital and nursing home services.

Despite these shocking figures, the outlook for the Nation's cardiovascular health is improving; death rates from coronary disease have been declining, falling about 34 percent from 1970 to 1984, and they are continuing to drop. At least two factors have probably contributed to this decrease—improved prevention in the general population and more effective therapy for individuals with known heart disease.

Coronary Artery Disease

The significantly improved prognosis over the past 15 years for those with confirmed coronary artery disease is the result of a number of advances in both medical therapy and surgical techniques. Understanding these advances depends upon understanding how the heart functions and how coronary artery disease develops.

The heart is a large, hollow muscle that pumps oxygen-poor blood through the lungs where the oxygen is replenished. The oxygen-rich blood returns to the heart, and is pumped back into the body through the aorta and the complex system of arteries that branch from it. All muscles in the human body, the heart included, require oxygen in order to function. Oxygen is supplied to the heart muscle by the two coronary arteries and their branches. These are the first offshoots of the aorta, and they lie on the outer wall of the heart. If the blood supply through a coronary artery is sufficiently reduced, chest pains (angina) often result. If the blood flow is cut off entirely, the part of the heart muscle supplied by the blocked artery may die. The death of heart tissue that results is called myocardial infarction or heart attack.

The narrowing and ultimate blockage of coronary arteries is the result of a slow process called atherosclerosis. In atherosclerosis, calcium and fatty materials in the blood, particularly cholesterol, are deposited on artery walls. Over a period of years, the deposits enlarge and thicken, forming plaques. The artery becomes rough, narrow, and hard—thus the popular name for atherosclerosis, "hardening of the arteries." For a number of reasons, blood clots are likely to form at the site of the narrowing. When a clot forms, blood flow through the artery may stop entirely, and a heart attack may occur.

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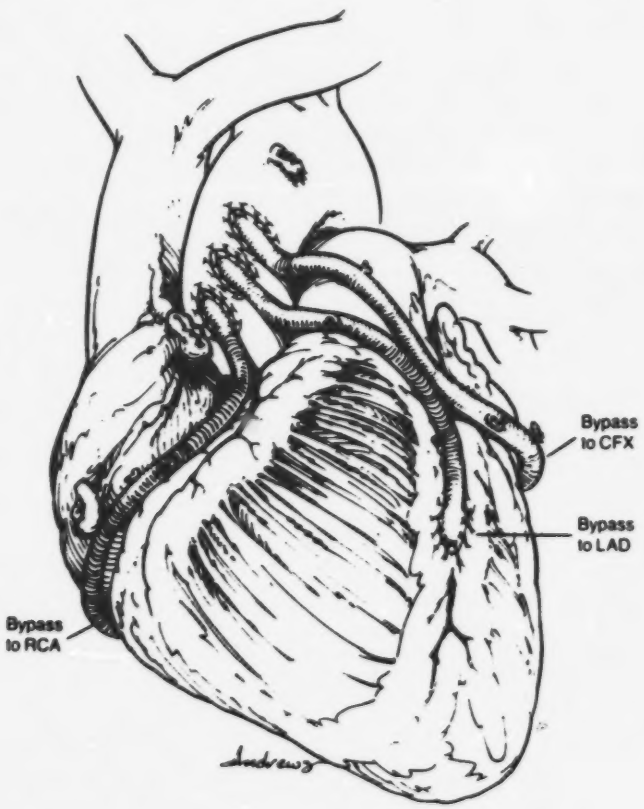
Although a heart attack is sudden, the buildup of plaque and scar tissue takes place over many years. Once atherosclerosis is severe enough that the individual is experiencing angina or is at risk for a heart attack, doctors may be able to intervene with drug therapy or surgical procedures to prevent or diminish the ultimate death of heart tissue.

Treatment of heart disease with medication has been bolstered by the use of two new families of drugs, beta blockers and calcium blockers. These, along with nitroglycerin (and other nitrates), either reduce the heart's demand for oxygen or increase the blood flow to the heart or both. Unfortunately, medication sometimes fails to relieve the symptoms in a number of individuals with heart disease. There are, however, several alternate treatments available.

Coronary Artery Bypass

The most commonly used alternative is the coronary artery bypass operation. In less than 20 years since the first bypass surgery was performed in 1964, the operation has become one of the most frequently performed in the United States (202,000 in 1984).

In the majority of cases, a saphenous vein is removed from the patient's leg. One end of the vein is attached to the aorta and the other end to the blocked artery at a point beyond the obstruction, thus bypassing it. This procedure is repeated for each affected coronary artery or major branch.



Coronary artery bypass. In this triple bypass, grafts were placed from the aorta to the occluded right, circumflex, and left anterior descending coronary arteries.

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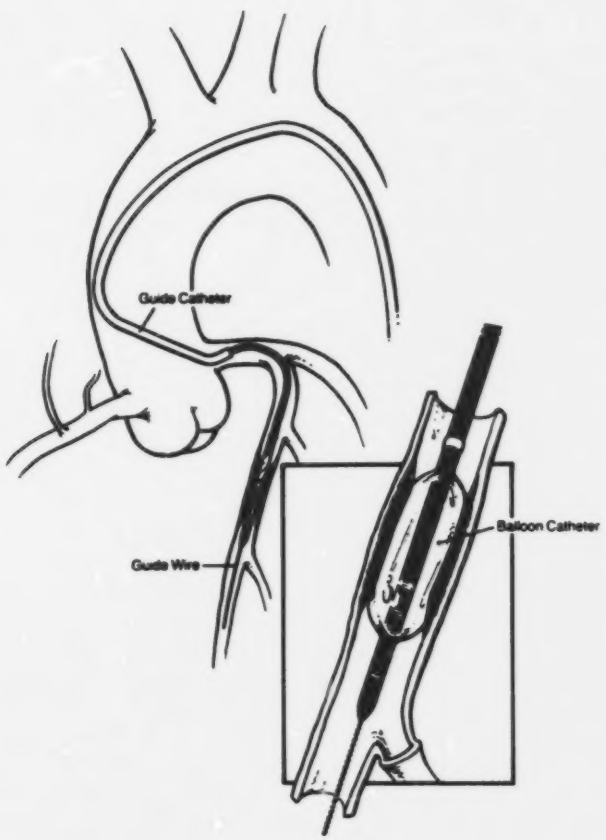
But long-term followup of patients with these vein grafts has shown that some grafts deteriorate, which may necessitate reoperation in some patients. Surgeons are, therefore, now turning to the use of the internal mammary artery found in the chest to bypass blocked arteries, since studies have found this conduit to be less prone to degenerative changes, including atherosclerosis. Use of this artery may significantly alter and reduce the incidence of reoperation following bypass surgery and may increase survival.

A high percentage of patients have complete relief from pain following bypass surgery. Many more experience marked improvement. In addition, there is increasing evidence that surgery prolongs the lives of individuals with certain types of coronary artery disease. Despite the effectiveness and increasing safety of the bypass operation, it is a major surgical procedure with attendant physical, emotional, and economic costs to the patient.

Percutaneous Transluminal Coronary Angioplasty

The development of less invasive treatments for atherosclerosis is continuing. Percutaneous transluminal coronary angioplasty (PTCA) is one such alternative to bypass surgery. Performed at academic medical centers since the late 1970's,the procedure has become widely available only in the last few years.



Percutaneous transluminal coronary angioplasty. A balloon catheter is guided to the site of the blockage, then inflated to push the plaque into the artery wall and reopen the vessel.

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In angioplasty, a tube or catheter with an inflatable balloon is inserted into an artery in the patient's arm or leg and advanced to the site of severe coronary narrowing. Inflating the balloon dilates the area of narrowing and reopens the vessel.

Although angioplasty is clearly less invasive than bypass surgery, the two are not simply alternate treatments for the same problem. In contrast to surgery, angioplasty is generally used on individuals with a localized, severe blockage in one or two coronary arteries. In addition, it is only useful when constrictions are accessible to the catheter; arteries that are too narrow or too winding are unsuitable. Because there is a risk that a patient undergoing angioplasty will need emergency bypass surgery, candidates for the procedure must also be potential surgical candidates. Approximately 66,000 coronary angioplasty procedures were performed in 1984. Efforts are now being made to determine the optimum requirements for selection of patients for angioplasty and those in whom bypass surgery is the procedure of choice.

Heart Transplantation

For some patients with end-stage heart disease, any type of corrective surgery may be inadequate to restore satisfactory heart function. Heart transplantation may be considered in these cases.

With the recent introduction of the new immunosuppressive drug cyclosporine, a new era in heart transplantation began. Enormous strides have been made. Endomyocardial biopsy, a catheter technique in which samples of tissue from the heart are obtained, has aided in the diagnosis of potential rejection of the transplanted heart. Thus, a procedure which just a few years ago was fraught with great uncertainty is now becoming an increasingly common and effective intervention for patients dying of heart disease.

Two-year-old girl who received a heart transplant when she was 8 months old.

The 2-year-old girl in the photograph is running, jumping, talking, and playing just like a normal youngster. She received her heart transplant when she was 8 months old and was suffering from advanced cardiac failure due to subendocardial fibroelastosis, a degenerative disease of the heart muscle. She has had only three episodes of rejection, all within 2 months of surgery, and has remained healthy on cyclosporine.

Not all heart transplant patients survive, but most do. Recently, the Battelle Institute published the results of the National Heart Transplantation Study, commissioned by the Department of Health and Human Services. The results of this study, which was based on 431 patients, provide a dramatic picture of the impact of human heart transplantation:

- The average age of recipients is 42 years, individuals in the prime of their productive years.
- Over 80 percent of all recipients are alive after 1 year.
- Over 50 percent of all recipients are alive after 5 years.
- Over 32 percent of all living recipients are back in the workforce.
- Of all surviving recipients, 67 percent are judged by their physicians to be in good health, with no present signs of cardiac disease.

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As heart transplantation becomes an increasingly accepted therapeutic modality for the treatment of end-stage cardiac disease, attention must be focused on the need for heart transplantation and the availability of donor hearts. Pooled data from various sources have estimated that every year, as many as 14,000 people in the United States between the ages of 10 and 54 could benefit from a heart transplant. However, only 1,900 are likely to be accepted for the procedure. As the lower and upper age limits for transplantation are eliminated, more candidates will qualify for transplantation. In 1985, approximately 627 heart transplant operations were done in the United States. The number of potential donor hearts is approximately 900 to 1,000 per year. Thus, although there has been technologic success in transplantation—capped by a remarkable reduction in the rates of rejection, infection, and death since the introduction of cyclosporine—the donor shortage in this country has not been overcome. More than 30 percent of those people waiting for a heart transplant die while they are waiting.

Multiple organ transplantation has emerged as a viable therapeutic approach since 1981. Simultaneous heart and lung transplantation is being done more frequently. Experience from all transplant centers shows a 55 percent survival for this more complex procedure.

Transplantation has today, in 1986, achieved its primary goals: to alleviate suffering and provide life where it could no longer exist; and provide quality rehabilitation for individuals, so that they can return to normal and productive lives with their families. This has been accomplished because the field of transplantation has encompassed a unique integration of surgical and immunologic disciplines that can now result in excellent rehabilitation. The magnitude of this accomplishment can best be appreciated by the fact that just two decades ago, almost all patients with end-stage heart disease died within a year.

Assist Devices and the Total Artificial Heart

Of those patients awaiting cardiac transplants, almost one-third die before a donor organ becomes available. In the National Heart Transplantation Study, the average length of survival was 41 days for patients who failed to receive a transplant. These facts have served to bring artificial organs out of the research laboratory—they have become a clinical reality, although technical sophistication and refinements are continually being made.

To date, most medical institutions have concentrated on the development of left ventricular assist devices (LVAD), pumps designed to augment the pumping action of the failing left or right ventricle. These intricate pumps are seen not only as temporary measures until a donor heart becomes available but ultimately as totally implantable, untethered, permanent blood-pumping devices.

Already, nearly 300 externally powered assist devices have been used to wean patients from heart-lung machines or rescue others from profound cardiogenic shock. Long-term survival rates approach 50 percent. More recently, the devices have been used successfully as temporary measures until transplantation. The Working Group on Mechanical

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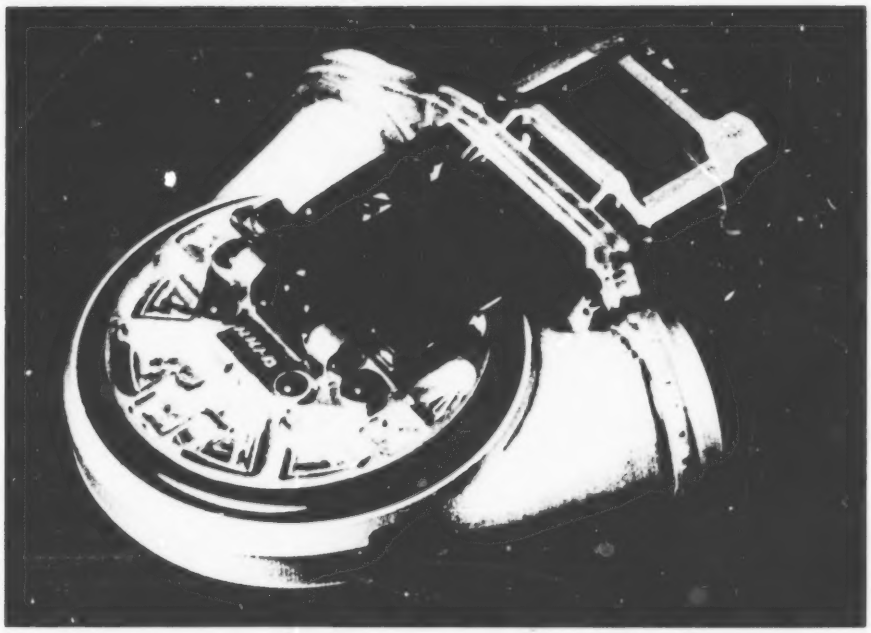
Left ventricular assist device



Circulatory Support, a team of experts commissioned by the Institute to study this field, estimates the potential number of patients who might benefit from a highly effective mechanical circulatory support system to be on the order of 17,000 to 35,000 annually. The group believes that fully implantable circulatory support systems will be available within 2 or 3 years and will provide at least 2 years of a good quality of life. They anticipate that recipients will be ambulatory and able to engage in moderate forms of exercise. The batteries for an electrically powered system will be rechargeable, anticoagulants will probably be needed, and medical surveillance will be necessary.

The man shown on opposite page is one of those sufferers of coronary artery disease who required more than a bypass operation. He had undergone bypass surgery in 1977, but his disease progressed; again he had chest pain, then terminal heart failure. A heart transplant was his only hope. However, his condition deteriorated while awaiting transplantation.

In an effort to save his life, surgeons inserted a left ventricular assist device (LVAD) to pump for his damaged left ventricle. This device is the product of over 10 years of funding by NHLBI. The LVAD totally maintained his systemic blood circulation for 8½ days, until a suitable donor was found and cardiac transplantation could be performed. This person is alive and well 1 year later because of the successful development of this device.

The quest for an artificial heart that is implantable, untethered, and "forgettable" is still under way. Devices currently under development will have a portable power supply to be worn on a belt or carried in a shoulder pack. The electrical power will be delivered through the skin, eliminating the need for any other tubes or wires from the body. The power supply will last for about 10 hours, allowing the patient complete freedom from a stationary source of energy for this period of time. The batteries will be rechargeable.

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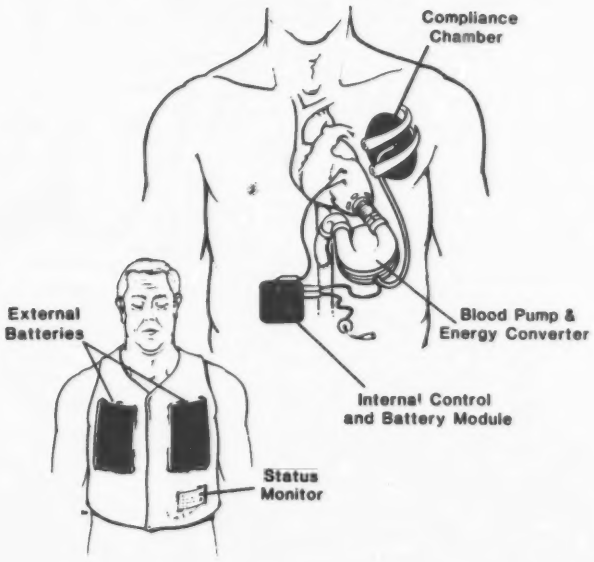
Patient who was kept alive with a left ventricular assist device for 512 days before receiving a heart transplant



Prototype for a totally implantable left ventricular assist system

Although cardiac transplantation candidates are currently the most likely potential recipients of the artificial heart, other potential candidates exist: those rare patients who cannot be weaned from the cardiopulmonary bypass machine after open-heart surgery because of preexisting heart disease, and for whom temporary left ventricular mechanical support would not be a viable option; and those who do not meet the requirements for heart transplantation.

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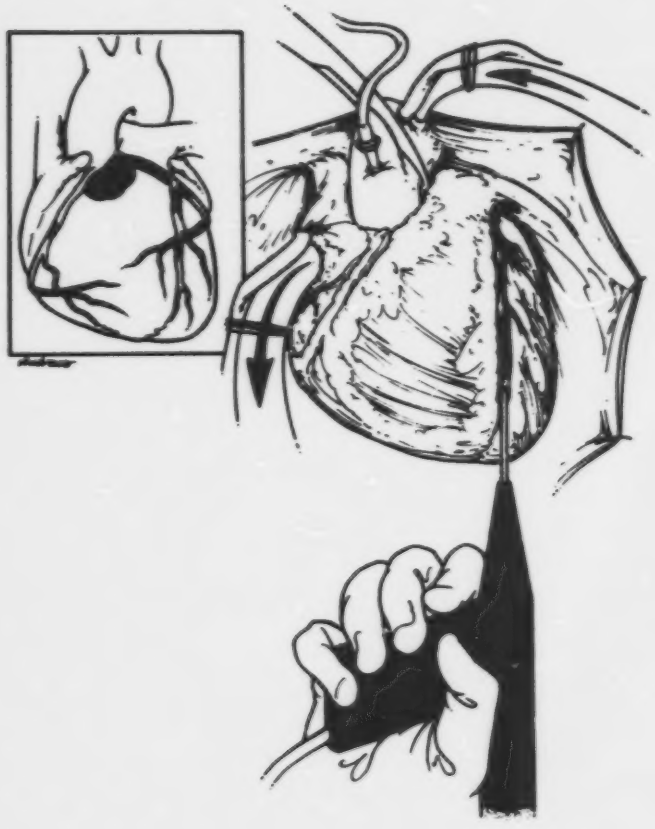
Sudden or progressive failure of the heart dooms to early death many persons whose health and mental capacities are otherwise sound. The concept of an artificial heart evolved out of the perceptions that the diseased human heart could be replaced by a mechanical device, and that through development of such a device, human life might be extended, the quality of life improved, and possibly years of productivity added.

The artificial heart and assist devices have gained their first steps toward acceptance as they have reliably extended the lives of human beings condemned otherwise to die. But efforts to extend life must include considerations of the quality of life, and thus a close relationship must exist between cardiac transplant surgeons and those involved with the artificial heart and other devices.

Other Clinical and Research Advances

Lasers. The word laser is an acronym for light amplification by stimulated emission of the radiation. Photons are emitted in the form of a laser beam from a stimulated laser medium, either solid or gas. The beam may be directed to its target by a series of mirrors, or it may be directed through a small flexible quartz fiber. For the most part, lasers work by heating tissue. When tissue is heated to 60° C, protein and nucleotide denaturation (change of their natural qualities) occur. At 100° C, vaporization occurs. Tissue contracts as the water is evaporated.



Hand-held CO_2 laser used to treat coronary stenosis (narrowing of heart vessels).

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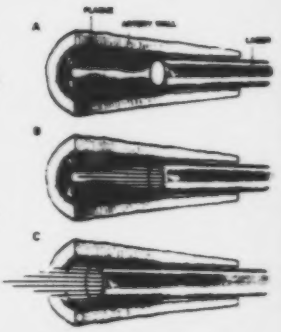
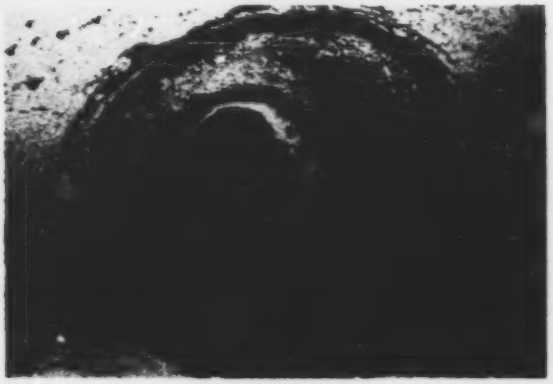
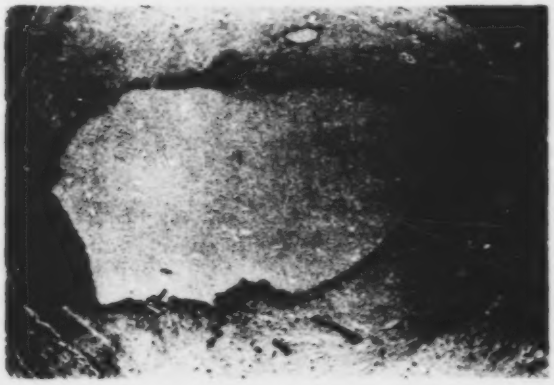
A number of applications exist for the laser. Laser-assisted microvascular anastomosis (welding of small blood vessels together) is being done experimentally and promises hope for the difficult repair of small vessels. Several cardiac repair procedures may eventually be done with laser techniques. Investigators also have reported that lasers are effective on myocardium and are now developing techniques of percutaneous transluminal antiarrhythmia procedures. The technique currently receiving the most attention, which has begun in clinical trials, is laser coronary endarterectomy, a technique that vaporizes plaque deposits from vessel walls and thus restores adequate blood flow.



Laser coronary endarterectomy: used to relieve coronary stenosis. Each laser impulse cuts a conical opening in the plaque.

A clinical trial was initiated at a major medical center in 1984 to determine the effectiveness of laser coronary endarterectomy for treatment of diffuse coronary atherosclerosis. The early results indicate patency in 28 of 30 bypassed arteries, 19 of 20 bypass grafts, and 12 of 16 laser-treated arteries. These results are promising and demonstrate the feasibility of laser endarterectomy for treatment of coronary atherosclerosis. Laser endarterectomy may prove to be a useful adjunct to the conventional bypass surgery in difficult anatomic situations or may supplant the need for bypass grafting in more localized lesions.





Left: Coronary artery prior to laser endarterectomy. The artery has extensive atherosclerotic plaque with a blood clot occluding the remaining channel.

Right: Results of laser endarterectomy on a critical coronary blockage. Laser endarterectomy doubled the open area of the artery.

Arrhythmias. The heart beats normally as a result of an intricate conduction system. When this system is abnormal, patients can suffer from incapacitating or life-threatening cardiac arrhythmias (abnormal heartbeats). Some of these patients may now be cured through a sophisticated combination of electrophysiologic mapping of the heart and state-of-the-art, open-heart surgical techniques. Technology currently available provides the clinician with the means to define precisely, locate anatomically, and ablate surgically the focus of a variety of serious cardiac tachyarrhythmias (fast, abnormal heartbeats).

Tachyarrhythmias in children differ from those in adults in a number of ways. Typically, the onset may be insidious, and symptoms may be confusing to the parent and pediatrician. Smaller children may be unable to verbalize their symptoms. In addition, some children may have a normal electrocardiogram between episodes, and this makes the diagnosis difficult to establish. Failure to cure the tachycardia can lead to incapacitating and dangerous arrhythmias or serious cardiomyopathy (a degenerative disease of the heart muscle).

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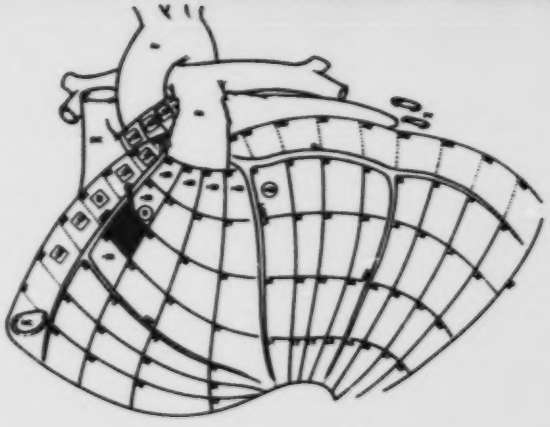
Investigators have demonstrated that infants and children at high risk of sudden death from tachycardia can be treated safely and curatively with surgery and intraoperative electrophysiologic mapping. Surgical procedures with predictable results are now available for a variety of childhood tachyarrhythmias. As an illustration, a 12-year-old girl was suffering from congestive cardiomyopathy and was almost bedridden. Her heart was dilated and had poor contractility, and the doctors were considering a heart transplant. However, because she also had tachycardia, electrophysiologic mapping was done to rule out the possibility of an abnormal conduction system. The study revealed a left atrial automatic-focus tachycardia. The focus was ablated by a freezing technique. Three years later, her heart size and function are totally normal. She has had no recurrence of tachycardia, and today is an active teenager.

Ventricular mapping being performed with fingertip probe on a two-year-old child with an abnormal heart beat called ventricular tachycardia.

Operative map demonstrating the site (D4) of earliest ventricular depolarization in a patient with Wolff-Parkinson-White syndrome. In this syndrome, patients have an abnormal conduction system that causes preexcitation of the ventricle and tachycardia. These patients can now be treated surgically when medication cannot control the condition.



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Abnormal cardiac rhythms in adults account for a large percentage of patients dying suddenly of coronary artery disease before reaching hospitals. Those people at highest risk are being defined by several large-scale clinical trials, and many new pharmacological therapies are being tested to prevent arrhythmias. In addition to using advanced techniques of surgical and catheter ablation, in difficult cases, surgeons have implanted improved devices designed to defibrillate the heart. These devices sense abnormal rhythms accurately and are being used to attempt to reverse the abnormal rhythms painlessly. These devices also provide a safety net during adjustment of medications allowing earlier discharge from hospitals. In addition, serial electrophysiological studies can be performed noninvasively to test the efficacy of each change in therapy.

The patient shown here suffered a myocardial infarction 2 years ago, and, except for two episodes when he was fortunately revived by rescue squads, remained symptom-free after bypass surgery. An implantable defibrillator now protects him from any future episodes. He has returned to a normal life style and has not needed to be hospitalized or assisted by a rescue squad for the past year.

After receiving an implantable defibrillator, this patient now leads a symptom-free, normal life.

Of course, coronary artery disease can strike a person at any age. The patient in the photograph below had sarcoidosis of the heart, suffering from arrhythmias of the heart and ventricular tachycardia at the age of 30, in the prime of his life. An implanted pacemaker corrected the blockage of electrical impulses between the upper and lower chambers of the heart, while experimental drugs controlled his ventricular tachycardia. The efficacy of drug changes was determined by serial electrophysiological testing using his implanted pacemaker. Once his rhythm was controlled, he was able to return to a relatively normal life style.

Cholesterol Metabolism. Lethal arrhythmias and other causes of death in coronary artery disease should be reduced in the long run by prevention of atherosclerosis. Several basic developments in cholesterol metabolism seem promising. Cholesterol is a fundamental building block for the membranes of all cells, for the synthesis of steroid hormones, and for bile acid metabolism, but it induces atherosclerosis when present in excess in the blood.

Patient who received a pacemaker and experimental drugs to control his heart's rhythm, has been able to resume normal activities.

Cholesterol is transported by large, specialized lipid and protein molecules (low density lipoproteins or LDL) in the blood and interstitial fluids. Cells take up the cholesterol by means of specialized binding sites on their surface that are called LDL receptors. The receptors and LDL are taken into the cell where the LDL is broken up, the cholesterol separated, and the receptors sent back to the cell surface to be reused.

The cell can also make cholesterol for itself at a rate that is limited by an enzyme called HMG CoA reductase. Thus, the cell has two sources for cholesterol. It has been found that cholesterol from outside the cell tends to decrease the synthesis of new cholesterol by HMG CoA reductase and also to decrease the production of LDL receptors. Similarly, a shortage of cholesterol for the cell will increase these processes. The study of certain genetic defects in receptor numbers or behavior has played a crucial role in understanding this system.

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The liver is a major site of LDL receptor expression. Its demand for cholesterol can be increased if a drain is placed on its manufacture of bile acids from cholesterol by increasing their excretion from the body with resins that sequester bile acids in the intestine. The liver responds by increasing LDL receptor numbers and synthesis of HMG CoA reductase. The receptor increase will remove more cholesterol from the blood, lowering its level, although this will be partially offset by increased synthesis of cholesterol by the liver. Recent results from long-term trials using resin to reduce cholesterol show a decrease in coronary artery disease proportional to the amount of cholesterol lowering achieved. Certain drugs, as yet experimental, can inhibit HMG CoA reductase. Bile sequestrants and HMG CoA reductase inhibitors can be employed together with reinforcing effect.

Many basic research issues arise from this body of work. For example, the LDL receptor belongs to a class of proteins that can migrate laterally very freely in the cell surface membrane and can leave the surface membrane to contact the membranes of certain organelles within the cell. A highly organized pattern of intracellular traffic is thus established as a phenomenon that integrates the cellular metabolism of cholesterol and also affects its extracellular homeostasis. Current and future researchers will seek to discover what dictates the mechanisms of cholesterol use and synthesis.

In addition, understanding the basic mechanisms of prostaglandin (certain fatty acids) synthesis may lead to the control of platelet aggregation and vascular tone, thus retarding or even preventing atherosclerosis. Population studies, for example, link the use of poly-unsaturated fish oils—omega 3 oils—with a reduction in the death rate from coronary artery disease. This appearently is the result of the direct effect of fish oils on pro-stag'andin synthesis and platelet aggregation. The mechanism of action is complex but becoming better understood. Low doses of aspirin also influence prostaglandin systhesis and platelet aggregation, which may explain why aspirin helps some patients with coronary disease. Researchers will continue to emphasize basic research to find ways ultimately to prevent atherosclerosis rather than just to improve a patient's comfort and longevity after a heart attack.

Conclusion

While heart disease remains a significant problem, fewer Americans have been dying of coronary artery disease over the last 15 years. Many researchers believe that changes in life style have contributed significantly to this decline. Certainly the American public is increasingly aware of the risk factors for heart disease, chief among them are high blood pressure, cigarette smoking, elevated levels of fat in the blood, diabetes, family history, stress, possibly obesity, and physical inactivity. These risk factors all contribute, in one way or another, to the process of atherosclerosis. Treating or correcting them can slow or in some cases reverse the process, thus reducing the incidence of heart disease.

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Future treatment of coronary artery disease will undoubtedly include additional approaches: new medications are constantly being developed, and innovations like laser surgery are already in use experimentally. But most doctors agree that prevention is the key. Local programs for education and cardiac rehabilitation are essential in the ongoing effort to control the Nation's number one killer.

Research and clinical trials will continue. Advances in immunology will allow transplant recipients to live longer and more productive lives. As cardiologists and cardiovascular surgeons refine techniques to help both adults and children with all forms of congenital and acquired diseases of the heart, the prognosis for heart disease will continue to improve.

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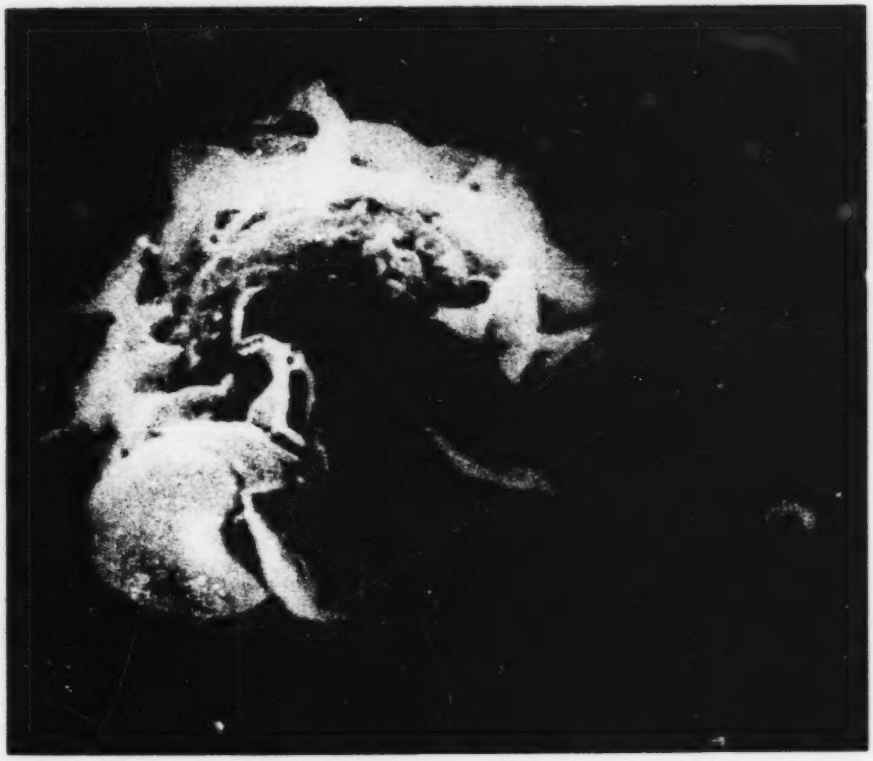
Introduction

Through its mandate, the Institute supports a varied research and training program whose goal is the treatment, cure, and ultimate prevention of lung diseases. This section focuses first on two such diseases—sarcoidosis and pulmonary fibrosis—and then briefly describes advances in several other areas.

Because the lungs are made up of several hundred thousand tiny air sacs, the internal surface area of lungs is huge, about half the size of a tennis court, and more than 70 times larger than the external surface area of the skin. Each day, an average adult will inhale nearly 3,000 gallons of air during normal activities, thereby exposing the delicate membranes of the lungs' interior to chemicals, toxic particles, or infectious microorganisms present in the environment. To protect themselves and the rest of the body, the lungs have two types of elaborate defense systems that remove or inactivate hazardous substances and germs. One of these systems is nonspecific and serves to protect against any foreign substance, regardless of its nature. The other system is highly specific and depends on immunologic defenses in which a variety of cells in the lungs and bloodstream participate.

As might be expected and as now is established by the results of recent investigations, these two systems do not function independently, but are linked by a network of chemical mediators that allows cells to communicate with each other. One of the key cells in this network is the alveolar macrophage. These cells are found in large numbers in the thin film of liquid that lines the air sacs. As macrophages patrol the vast alveolar surface, they ingest (phagocytize) bacteria or foreign particles and thus rid the body of these potentially harmful substances.



Macrophage engulfing bacteria.

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Because they are situated within the air sacs, alveolar macrophages can be washed out of the lungs of normal persons as well as of patients with various forms of lung diseases by a simple technique known as alveolar lavage. With this technique, the airways and air sacs are bathed or washed with a fluid that is then retrieved. Studies of the alveolar macrophages recovered by lavage have shown that these cells do much more than just phagocytize and eliminate particles. They locate and process foreign materials called antigens as the first step in mounting an immune response directed against the antigens. Alveolar macrophages also synthesize a variety of mediator substances that have potent biologic effects. The results of recent research sponsored by the NHLBI have provided new insights into how these remarkable biochemical factories not only protect the body but also, under certain circumstances, contribute to the development of granulomatous and fibrotic lung diseases such as sarcoidosis, hypersensitivity pneumonitis, berylliosis, silicosis and pulmonary fibrosis (excessive amounts of fibrous tissue and scarring). These diseases are characterized by the formation of granulomas (grainy nodules of inflamed tissue), scarring or both; they occur in both occupational and nonoccupational settings, and are a major cause of morbidity, mortality, and socioeconomic cost.

Sarcoidosis

Sarcoidosis is a disease characterized in its early stages by the formation of granulomas. When extensive, these tiny nodules may cause symptoms such as shortness of breath. For example, the school teacher shown here had been in excellent health until she started to notice shortness of breath, especially during exercise. When she could no longer play tennis, she went to her physician who gave her a series of tests, including a bronchoscopy for removal of a few small pieces of lung for microscopic inspection and culture. Examination of these specimens revealed multiple granulomas, a finding typical of sarcoidosis.

Patient (school teacher) having her lung capacity tested after being successfully treated for sarcoidosis.

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Although the lungs are the most common site of involvement, the granulomas of sarcoidosis may also form in the eyes, skin, brain, or heart. If untreated, the granulomas may evolve into extensive scar tissue within the lungs or other organs that causes severe and permanent disability. The school teacher, however, was treated with prednisone, which is a corticosteroid (a hormone-like drug) that causes granulomas to resolve, and she improved rapidly. She was able to resume playing tennis. One year later, the treatment was stopped and she has remained well.

It is now recognized on the basis of evidence from experimental animals that granuloma formation is the expresssion of a series of complex events involving two specialized cells, macrophages and T-lymphocytes (T cells). Both of these cells secrete soluble substances called mediators that affect how they and the other cell types function.

One of these mediators is interleukin-1, which is produced by activated macrophages and which amplifies T-lymphocyte-dependent immune responses. In addition to T cell activation, interleukin-1 has also been shown to stimulate T cells to produce interleukin-2, once they have been attracted to the site of the immune reaction. Interleukin-2 causes additional susceptible T cells to proliferate. These interactions reinforce each other and thereby provide a potent way of amplifying the initial phases of the immune response.

This experimental knowledge has now been applied to achieve a better understanding of granuloma formation in active sarcoidosis. Lymphocytes lavaged from the lungs of sarcoidosis patients, in contrast to lymphocytes from patients with other pulmonary diseases, spontaneously release interleukin-2 as well as macrophage migration inhibitory factor, a mediator that inhibits movement of macrophages. It seems clear that these and other cellular mediators are important in the formation of granulomas in patients with sarcoidosis and other related diseases. But what triggers the response in the first place, and what causes it to subside in some patients, such as the school teacher, but to progress to fibrosis in other patients are important questions that await further study.

Pulmonary Fibrosis

Fibrosis of the lungs is analogous to scar tissue anywhere in the body in that once fibrosis occurs, it is irreversible. Scars may occur in the lungs after a wide variety of damaging insults such as tuberculosis and other chronic infections. Usually, once any of these causes is recognized and treated, the stimulus for scar formation is eliminated and no further fibrosis occurs.

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Patient (truck driver) suffering from pulmonary fibrosis.

In contrast to pulmonary fibrosis of known origin that can be arrested, there is a form of this disease which characteristically progresses to severe disability and even death and for which no cause can be identified. This form of pulmonary fibrosis afflicted the truck driver shown here, who had been in exceptional health and was able to carry out the heavy physical labor required by his job without complaint. Then came steadily worsening periods of breathlessness. A variety of laboratory tests were normal, but breathing studies revealed a marked reduction in the patient's lung capacity and an abnormality in the oxygenation of his blood that became worse when he exercised. An operation was performed at which a piece of his lung was removed for microscopic examination, bacterial and fungal cultures, and other special tests. The specimen showed diffuse scarring of the lungs, but no specific cause for the process could be identified. Since then, despite treatment with corticosteroids, the patient has been unable to return to work and his condition has gradually deteriorated. Unlike sarcoidosis, pulmonary fibrosis seldom responds to any form of treatment.

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When viewed through the microscope, fibrosis of the lung consists of abnormal accumulations of connective tissue in which two components can be recognized: (1) the dense matrix of organized collagen and elastin fibers that forms the bulk of the scar, and (2) fibroblasts, the cells that actually produce the inert ingredients of the matrix. Macrophages also are usually present in varying numbers.

The role of macrophages in stimulating the synthesis of collagen has been the focus of a number of studies during the past few years. Several investigators have established that macrophages produce a growth factor for fibroblasts, commonly referred to as macrophage-derived growth factor. This substance stimulates the rate of replication of fibroblasts grown in tissue culture.

Recently, a second macrophage-derived modulator of collagen synthesis was identified. Using an animal model, researchers noted that pulmonary fibrosis formed in response to the antitumor drug bleomycin. After administration to hamsters, bleomycin induced fibrosis that was associated with an initial collagen accumulation resulting from an increase in the rate of collagen synthesis, followed by a decline toward normal collagen synthesis a few weeks later. By isolating macrophages from bleomycin-treated animals when collagen synthesis began declining and growing them in culture, scientists identified a macrophage-derived suppressive factor. This suppressive factor apparently regulates the return of collagen synthesis to normal. The suppressive factor was heat stable, had a molecular weight of 20,000 to 30,000 daltons, suppressed human as well as hamster fibroblasts, and was selective for collagen synthesis inhibition, since collagen production was decreased more than noncollagen protein synthesis. These results suggest that suppression of collagen synthesis is important in regulating collagen production and ultimately in limiting collagen accumulation in response to injury. The failure to inhibit collagen production appropriately following injury could contribute to the excessive accumulation of collagen that is characteristic of pulmonary fibrosis.

The results of these and many other studies indicate that cells communicate with each other by synthesizing and releasing potent mediators into their local environment. These mediators attract effector cells to the region and stimulate them. Normally, this process is carefully regulated by a delicate balance between activator and inhibitor substances. When out of balance, exuberant cellular activities cause pathologic abnormalities of the lungs such as granulomas or fibrosis.

Much more fundamental research is needed to provide a full understanding and identification of the biochemical signals that affect cell-to-cell interaction, and how these messages are translated at the molecular level by the affected cells. But the clinical implications that derive from this knowledge are of enormous benefit. Knowing more about the mediators that participate in lung defenses and tissue repair will allow physicians to control the many disabling lung diseases such as sarcoidosis and pulmonary fibrosis, that are characterized by the formation of granulomas and uncontrollable scarring.

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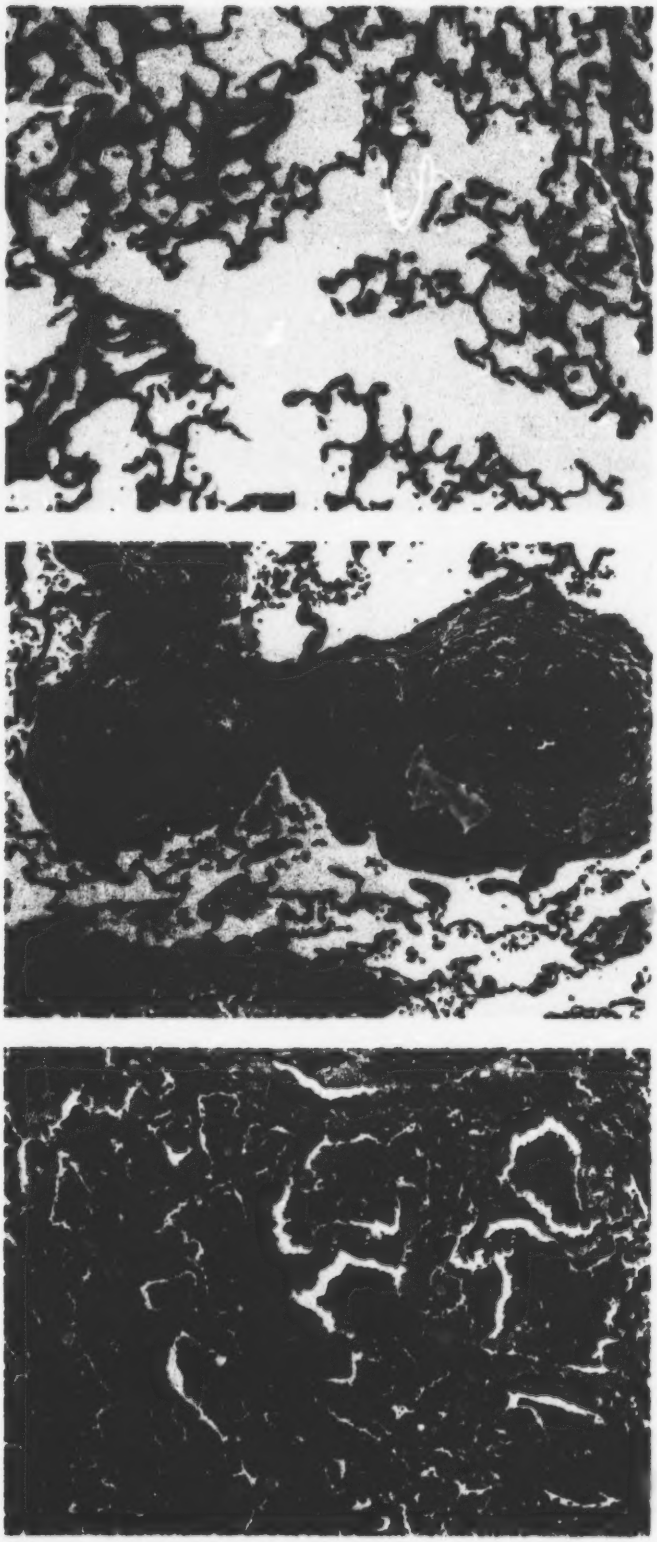
Electron micrograph showing normal lung tissue (top) contrasted with those of patients suffering from sarcoidosis (middle) and pulmonary fibrosis (bottom)—diseases that are characterized by the formation of granulomas and uncontrollable scarring.



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Highlights of Scientific Progress in Other Areas of Lung Disease

Lung Surfactant and Neonatal Respiratory Distress Syndrome. Truly remarkable advances have been made in understanding the composition, function, and physiochemical properties of lung surfactant, the lipoprotein substance that lowers surface tension in the lungs and prevents collapse of the alveoli (the smallest air sacs) after each breath. These advances have led to improvements in the prediction, management, and treatment of neonatal respiratory distress syndrome, a disease characterized by a deficiency of normal surfactant.

Researchers have uncovered the molecular and cellular mechanisms regulating surfactant and its actions; but intensive investigations on the chemical, physical, and biological factors that determine the adequacy of its function suggest that control of the surfactant system may turn out to be much more complicated than was previously thought. Understanding the functional significance of surfactant is of increasing interest because of the possibility of using artificial or animal-derived surfactant to treat diseases associated with surfactant deficiency. Many of these surfactant preparations now under study contain small amounts of protein. And yet, virtually no information exists on the potential immunologic consequences of administration of microgram amounts of foreign protein into sick, immature infants. If these proteins are essential for surfactant function, it is likely that human proteins produced by molecular biology techniques and subsequently purified would be the preferred coingredient with surfactant lipids for use in replacement therapy.

It is, therefore, of considerable interest that investigators have recently cloned the gene for human surfactant. By implanting the cloned gene in human cells, scientists can now synthesize large quantities of surfactant protein. This will allow them to develop molecular probes to determine the structure and regulation of the gene or genes responsible for encoding surfactant protein, to study gene expression during lung development, and to generate human surfactant-associated protein for possible clinical use.

Cystic Fibrosis. Cystic fibrosis is the most common lethal genetic disorder in the Caucasian population. Many patients die before the age of 20. While it is recognized that the disease is a result of one or more inborn errors of metabolism, the basic genetic defect remains unknown. Scientists have, therefore, concentrated their efforts at finding a biochemical marker associated with the gene in order to help them find the defective genetic material. Possible defects in ion transport across respiratory and other epithelial cells are being explored for clues to understanding the pathogenesis of this fatal disease.

In 1985, a quantum leap was made toward identification of the abnormal gene responsible for cystic fibrosis as a result of family studies of individuals who inherited the cystic fibrosis gene from a common ancestor. Using elegant molecular genetic techniques, researchers have located linkages to the cystic fibrosis gene on the middle portion of the long arm of chromosome 7, thus leading to the hope that it will soon be possible to identify and isolate the gene responsible for the defect.

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Cystic fibrosis patient undergoing pulmonary testing.

This exciting development should hasten the prospect of identifying the basic defect in cystic fibrosis, of providing genetic counseling to families by detecting carriers of the cystic fibrosis gene, and of developing methods for prenatal diagnosis. Although this important discovery will not immediately lead to any new therapy for victims of this disease, it will certainly add cystic fibrosis to the list of genetic diseases that may theoretically be prevented or cured with genetic engineering or gene replacement.

Chronic Obstructive Pulmonary Disease. Studies over the past 20 years have fostered a dramatic improvement in our understanding of the disease mechanisms underlying pulmonary emphysema with the finuing that a genetic deficiency for alpha-1-protease inhibitor, a protein circulating in the blood, is linked to the destruction of alveolar structures. The risk of developing this disease is directly related to the severity of the alpha-1-protease inhibitor deficiency. It is also now recognized that neutrophil elastase (a white blood cell enzyme) is inhibited by alpha-1-protease inhibitor, and destructive lung disease can be experimentally produced in animals by instillation of human neutrophil elastase into their lungs. From these and other observations, scientists believe that the lung destruction associated with alpha-1-protease inhibitor deficiency results from the unimpeded action of neutrophil elastase on elastin, an important structural component of the lung connective tissue.

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Children with asthma are instructed how to manage their condition.

Scientists have also demonstrated that cigarette smokers who suffer from emphysema have an increased level of neutrophils in their lungs. These neutrophils can cause connective tissue damage by releasing enzymes, especially elastase, which dissolve the elastic fibers. In addition, scientists found that the lung destruction can occur in individuals with normal levels of alpha-1-protease inhibitor if they smoke cigarettes, because of the inactivation of this protein by oxidants present in cigarette smoke or released by activated neutrophils during inflammation.

Recently, through genetic engineering, scientists have developed a modified form of alpha-1-protease inhibitor that is resistant to oxidative inactivation. Because of its resistance to oxidation, this mutant protein may be able to provide an antiprotease shield during inflammatory episodes and may have therapeutic implications for individuals with a genetic deficiency for alpha-1-protease inhibitor. Further study of this potentially lifesaving substance is needed.

Asthma Self Management. Under an Institute-sponsored educational program, children with asthma and their families have been taught how to manage this condition. They have learned what to do in case of an asthma attack, how to make decisions about activities that might cause an asthma attack, how to communicate with doctors and other health care providers, and how to solve the daily problems faced by those who suffer from asthma.

Thus far, the program has been developed for use in large cities, and has been evaluated in four inner-city hospitals in New York City with 310 asthmatic children and their parents. The results showed that for children who had been hospitalized once in the year prior to the program, emergency room use was cut in half. In fact, the number of hospitalizations decreased substantially for all participating children. These measures, however, remained constant for the children who were not part of the program. The estimated savings in health care costs were $14.58 for every $1.00 spent on education.

Programs such as this one are also being tested in various other geographical settings. Results indicate that for all groups, hospitalizations, emergency room visits, and days lost from school can be substantially decreased if children and their parents are educated in methods for the self-management of asthma.

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Blood Diseases And Resources

Introduction

The NHLBI supports a wide range of programs in the area of blood diseases and blood resources: hemostasis and thrombosis, which includes bleeding disorders such as hemophilia, as well as abnormal blood clotting that can lead to heart attack and stroke; red blood cell disorders and disorders of hematopoeisis (blood cell production); disorders involving abnormal hemoglobin structure or production, such as sickle cell anemia and Cooley's anemia; and blood resources, whose objective is to assure a safe and adequate supply of blood products. These programs achieve their goals by supporting investigator-initiated research grants, training and career development grants, large specialized centers, and research contracts.

The impact of blood diseases on the Nation's health is enormous. The sections below describe only a few of the many examples of how research supported by the NHLBI has helped individuals with blood diseases.

Sickle Cell Anemia

With advances in sickle cell disease research and improved medical care, the young boy with sickle cell anemia shown here can live into adulthood and probably to middle age. He was diagnosed at 1 year of age and is one of the more than 50,000 black Americans with sickle cell anemia. Many of these patients have only mild symptoms, while others like this young boy may require repeated hospitalizations for a variety of complications. The costs for patients in terms of medical care, insurability, lost employment, and underachievement of educational and career goals often place a large financial and psychological burden on both the patients and their families. The NHLBI supports a broad program in sickle cell disease designed to decrease the morbidity and mortality from this disease. This includes research and development at both basic science and clinical levels; programs in screening, counseling, and improved management of patients with sickle cell anemia; and programs to educate the community and medical and allied health professionals. The 10 comprehensive centers in sickle cell disease, mandated by Congress, form a national framework for carrying out these programs.

One of 50,000 black Americans suffering from sickle cell anemia.

The cause of sickle cell anemia is now well understood at the molecular level. The disease results from the substitution of one amino acid for another at a particular location along the hemoglobin molecule. Like all proteins, hemoglobin is constructed of a linear array of amino acids, which are arranged like beads of different colors on a string. Substitution of the wrong "color" bead at one location results in an abnormal hemoglobin molecule (termed hemoglobin S), which is "sticky" and polymerizes to form long rods. The rods deform the red cell and cause the red cell to take on its characteristic sickled shape, especially when the cell is exposed to low concentrations of oxygen. The sickled cells, which are unable to pass through small blood vessels, occlude the blood vessels, depriving the tissues of blood and oxygen. Recurrent painful episodes may result. Other complications of sickle cell disease include chronic anemia, increased susceptibility to infection, especially pneumococcal pneumonia and

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septicemia (serious blood infection), stroke (usually in young children), and chronic bone and joint disorders. Repeated blood transfusions used to treat these complications may lead to chronic iron overload, eventually causing liver disease or heart failure. These are some of the reasons for the pressing need for more research into effective ways to treat this disease.

No known drugs prevent or alleviate sickle cell crises safely and effectively. Several therapeutic approaches, however, have been suggested: 1) to inhibit the polymerization of the abnormal hemoglobin S molecule; 2) to alter the properties of the red cell membrane to make the cells less likely to sickle; or 3) to increase the red cell's ability to "turn on" the production of hemoglobin F (fetal hemoglobin), thus interfering with sickling.

One approach involves the design or selection of compounds that, when bound to the sites of contact on the hemoglobin molecule, would prevent hemoglobin S polymerization. Two independent investigators working collaboratively have used x-ray crystallography and computer-assisted imaging techniques to determine the binding sites of two very potent antisickling agents: ethacrynic acid, which is a diuretic, and an investigative nondiuretic derivative. These studies have suggested possible molecular mechanisms of action for the antisickling properties of these drugs, and may aid in the design of new drugs for clinical use.

Structure of hemoglobin. The hemoglobin molecule is composed of four chains of amino acids, two alpha chains and two beta chains. Each chain contains a heme group and an atom of iron, represented here as a plate and ball respectively.

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A new initiative for FY 1986 would encourage studies on the insertion and regulation of hemoglobin genes in red blood cell precursors. Several years ago, investigators were confident that disorders of hemoglobin synthesis, like sickle cell disease, would be among the first diseases to be treated by gene therapy (the insertion of genetic material into defective cells to correct congenital biochemical disorders). However, hemoglobin is a complex molecule composed of two chains, alpha and beta. The genes corresponding to these proteins are located on different chromosomes. The way in which precisely matching amounts of the alpha and beta chains are synthesized is poorly understood. This will be an insurmountable problem in the application of gene therapy unless a major effort is made to understand the regulation of human globin synthesis. This initiative will facilitate research on globin gene regulation at a time when many laboratories have switched to the study of less complex systems.

Bone Marrow Transplantation for Congenital and Acquired Blood Disorders

Bone marrow transplantation has gained acceptance in recent years as treatment for a number of congenital and acquired blood disorders that had previously resisted therapy. These types of disorders include, among others, aplastic anemia, leukemia and other hematologic malignancies, and severe combined immunodeficiency disease (the "bubble boy" syndrome). Until a few years ago, a successful bone-marrow transplantation required a sibling donor who was HLA (histocompatibility antigen)-identical, but recent results have been somewhat encouraging with siblings who are matched at only some of the HLA antigens. Another serious problem of transplantation has been graft-versus-host disease, which occurs when donor cells (the graft) immunologically attack host tissues. New immuno-suppressive agents such as cyclosporine and new methods of preparing donor cells to eliminate the attacking cells have led to improved results and to the wider acceptance of bone-marrow transplantation. Approximately 8,000 marrow transplants have been performed worldwide since 1970.

The patient pictured here had severe combined immunodeficiency disease, which is characterized by the lack of both humoral (antibody-mediated) and cell-mediated immunity. For such individuals, the most trivial infection often became life-threatening, and they rarely survived beyond 1 year without extraordinary precautions, such as the provision of a germ-free environment. This young man, however, received a bone marrow transplant from his HLA-matched sister. As a result, 17 years later, he is in excellent health and is a good football player. For such fortunate individuals, bone marrow transplantation restores immune competence, allowing them to resume a normal life.

Patient leads normal, healthy life after receiving bone marrow transplant from HLA-matched sister.

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Highlights of Scientific Progress in Other Areas of Blood Diseases and Resources

Young hemophiliac patient injecting himself with Factor VIII, a plasma clotting protein.

Hemophilia. One of the most common genetic bleeding disorders, hemophilia A, is caused by defects or deficiencies in a plasma clotting protein, factor VIII. Patients with hemophilia must receive injections of plasma concentrates containing this factor to control episodes of spontaneous bleeding or to undergo surgical procedures. Most patients learn to administer the medicaitons to themselves. Early and intensive use of these plasma concentrates has led to an improved quality of life for hemophiliacs; for example, unemployment among adults was 13 percent in 1984, compared to 36 percent before home treatment became common during the 1970's. There has also been an 86 percent reduction in hospitalization and a 62 percent decrease in medical costs during this same period.

The plasma concentrates used to supply factor VIII are obtained from blood donors. However, each batch of concentrate is prepared from plasma obtained from between 2,500 and 25,000 donors. A hemophilic may use concentrate from as many as 5 to 10 different batches in any one year. Therefore, the risk of exposure to viral hepatitis, AIDS, and other plasma-transmitted diseases has been high.

But the situation is improving. Methods have been found to inactivate a large portion of some types of viruses including the AIDS virus, in these concentrates. Even more promising is the application of techniques of molecular biology to this problem. Scientists can now prepare pure human clotting factors by genetic engineering methods rather than by isolation from blood. The availability of human factor VIII produced by genetic engineering will eliminate the risks of viral disease transmitted by blood products.

Electron micrograph of a human platelet, an element of blood that is essential to blood coagulation or clotting. (C = conaliculus, or small channel, G = granule, IF = inner face, OF = outer face)

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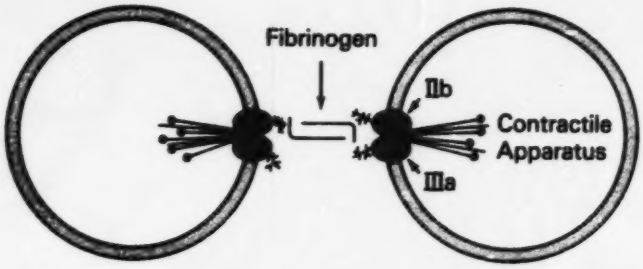
Regulatory proteins in hemostasis and thrombosis. In the circulation, the clotting process is usually self-limiting and highly localized. An intricate biochemical pathway has recently been described to explain this phenomenon. The pathway involves two newly characterized plasma proteins, protein C and protein S, and thrombomodulin, which is a receptor on the surface of blood vessel walls. When the coagulant enzyme thrombin binds to the receptor thrombomodulin, its specificity is changed, so that instead of activating coagulation, it activates protein C. Protein C then forms a complex with a "helper" protein S, and the complex destroys some activated clotting factors. The complex also diminishes the authority of an inhibitor of plasminogen which activates a potent clot-lysing agent. This complex chain of events leads to strong inhibition of clot propagation at the site of blood vessel injury.

Patients with inherited deficiencies of proteins C and S are believed to be at greater risk of thrombosis. A few patients with severe (homozygous) deficiency of protein C have been successfully treated by infusions of concentrates containing protein C. Other clinical uses for these newly found anticoagulant substances are only beginning to be explored, but they offer the promise of control over blood clotting processes not previously possible.

Platelet surface glycoproteins in congenital bleeding disorders. Blood platelets are tiny cellular fragments that play a critical role in controlling bleeding whenever a blood vessel is injured. Platelets exposed to the cut surfaces of blood vessel adhere to each other and form a hemostatic "plug," which limits blood loss. Defects in platelet proteins lead to congenital bleeding disorders such as Glanzman's thrombasthenia, Bernard-Soulier syndrome, and the gray-platelet syndrome. Bleeding manifestations range from minor to life threatening. Our understanding of these disorders has been advanced by the study of certain molecules, called glycoproteins, on the surface of platelets. Two of these glycoproteins, designated IIb and IIIa, have recently been shown to play a fundamental role in platelet function.



Function of platelet glycoproteins IIb and IIIa. Glycoproteins IIb and IIIa serve as a bridge between a blood protein, fibrinogen, on the outer surface of the platelet and a contractile protein, actin, on the platelet's inner surface. Improved understanding of platelet surface glycoproteins may lead to improved treatment of congenital bleeding disorders.

Platelets from patients with Glanzman's thrombasthenia lack glycoproteins IIb and IIIa. These platelets cannot aggregate in response to thrombin, collagen, or ADP, which are normal stimulants for platelet aggregation. Additional studies indicate that the IIb-IIIa complex functions as a bridge between fibrinogen on the outside of the platelet and contractile proteins on the inside of the platelet, allowing the clot to retract after it has formed. Clot retraction may be important for hemostasis and healing of the

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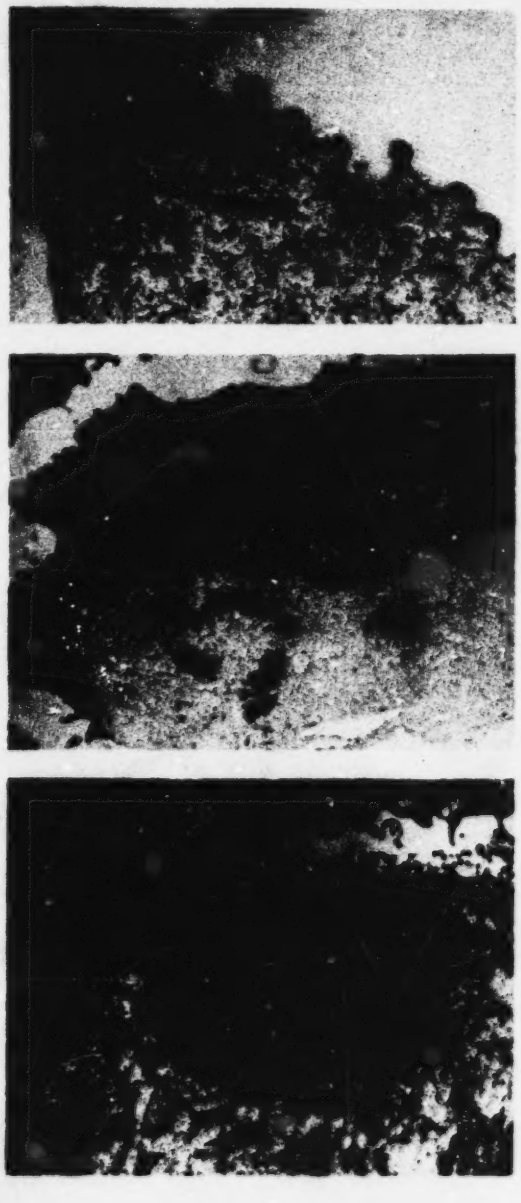
breached blood vessel. The study of platelet surface glycoproteins has led to improved understanding of normal blood clotting and the congenital platelet disorders.

Transfusion-transmitted diseases. Few people are unaware of the enormous impact that acquired immune deficiency syndrome (AIDS) has had on health resources in the U.S. Over 16,000 AIDS cases have been reported between 1981 and January 1986 in the U.S., and the number of reported cases is expected to double in 1986. About half of these patients have already died. From work supported by the National Cancer Institute, scientists have discovered that the cause of AIDS is the human T-lymphotropic virus type III (HTLV-III), also known as the lymphadenopathy-associated



Cultured mononuclear cells infected with an AIDS-associated virus: viral particles on the surface of a cell (top); the cell undergoing mitosis (cell division) with viral particles budding from the plasma membrane (middle); and enlargement of the budding viral particles (bottom).

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virus (LAV). In a relatively small number of cases—approximately 1 percent of AIDS patients—this virus has been transmitted from infected blood donors to recipients of blood products. (Of course, blood donors cannot themselves get AIDS from giving blood.) Since March 1985, blood and plasma-collection centers have adopted a screening procedure that will virtually eliminate transmission of AIDS through blood products. Test kits are now available to detect antibodies to HTLV-III in blood; these test kits are highly sensitive. The NHLBI has supported the implementation and validation of these test kits. It is estimated that between March and August 1985, screening procedures have removed about 1,000 potentially infectious units from the U.S. blood supply, thereby greatly reducing the risk that previously existed.

A second transfusion-transmitted viral disease is cytomegalovirus (CMV), which usually produces minor infection in normal adults and children, but can produce serious or fatal pulmonary, renal, heart, or liver infection in immunosuppressed individuals such as recipients of transplants, some cancer patients and some infants. Premature infants who require multiple blood transfusions have a 15 to 30 percent incidence of CMV infection, with a mortality of 20 percent. One study has shown that 40 percent of blood donors have evidence of CMV infection and that 10 percent of such donors appear to transmit the virus. There is no means to prevent or treat CMV infection. Therefore, the NHLBI is supporting a randomized, controlled trial on the effectiveness of a cytomegalovirus immune globulin to protect against CMV in high-risk infants. Preliminary results of this study are encouraging.

Young patient with Cooley's anemia receiving a blood transfusion. The Institute's efforts to ensure an adequate and a safe supply of blood resources are vital for such individuals who need frequent blood transfusion.

Transfusion medicine. During the past fiscal year, three specialized centers of research in transfusion medicine were funded, and the multidisciplinary, basic and clinical research at these centers has now begun. There have also been an increasing number of grants awarded in this area. An additional development was the Transfusion Medicine Academic Award, which enables medical schools to develop curricula and a cadre of trained medical personnel in transfusion medicine. Thus, the NHLBI has not only a viable but also an aggressive and a potentially productive program underway to encourage the appropriate and effective use of our country's blood resources.

Through the varied research programs the NHLBI supports in transfusion-transmitted diseases, hemophilia, bone marrow transplantaiton for congenital and acquired blood disorders, sickle cell anemia, and other areas of blood diseases and resources, the Institute hopes to help bring about the day when all suffering caused by these blood diseases is history.

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PRIORITIES, GOALS, AND RESOURCES

Introduction

In this report, the Council has emphasized the individual patient, and has brought to your attention the impact of clinical advances and biomedical research supported by the NHLBI on the lives of several people and their families. Continuing to find new ways to treat, cure, and prevent diseases such as the ones afflicting these individuals is the main goal of the Institute.

This report would not be complete without mentioning with pride this year's Nobel Prize winners who have had a close association with the Institute. Dr. Michael S. Brown and Dr. Joseph L. Goldstein, two Americans, won the 1985 Nobel Prize in Physiology or Medicine for discoveries in cholesterol metabolism and the treatment of cholesterol-related diseases. Both scientists worked in the NHLBI intramural program between 1968-1971 and since then have been supported by the Institute. In a letter to Dr. Claude Lenfant, Director of the Institute, thanking the Council for their letter of citation, Dr. Brown and Dr. Goldstein stated, "As you know, the National Heart, Lung, and Blood Institute has been the source of almost all of our funding for the work that was honored. We are deeply grateful for the broad vision of the Council over the years in supporting basic research that may not appear directly related to heart disease. It is this foundation of basic research that will allow real clinical progress to be made."

Also to be congratulated is Dr. Bernard Lown, who was one of the cofounders of the International Physicians for the Prevention of Nuclear War. The goal of this worldwide federation of doctors and health professionals is to publicize the danger of nuclear weapons. The International Physicians for the Prevention of Nuclear War Organization was awarded the 1985 Nobel Peace Prize. Dr. Lown is an eminent cardiologist and has been a research grantee of NHLBI for many years. The 1985 Nobel Prize in Chemistry was shared by two Americans, Dr. Herbert A. Hauptman and Dr. Jerome Kale. Dr. Hauptman has also been supported by the Institute.

The Council congratulates all these 1985 Nobel Laureates, and notes with pride that 16 grantees of this Institute have received Nobel Prizes since NHLBI was created.

Funding Information and Award Rates

As has been the case in recent years, the Institute has not been able to fund a sufficient number of meritorious applications because of budgetary limitations. The figure entitled "NHLBI Competing Research Project Grants: Applications Reviewed, Eligible for Award, and Awarded: Fiscal Years 1970-1985" illustrates this fact graphically. While the number of grant applications reviewed and those eligible for funding (rigorously reviewed and favorably recommended as being scientifically meritorious and worthy of support) has risen dramatically during these 10 years, the number of awards has not followed a similar pattern. The result has been a widening gap between meritorious applications and actual awards. Thus, in fiscal year 1972, 70 percent of the research project grants eligible for funding were actually awarded; by fiscal year 1985 the percentage had fallen to 37 percent. The budget of the Institute

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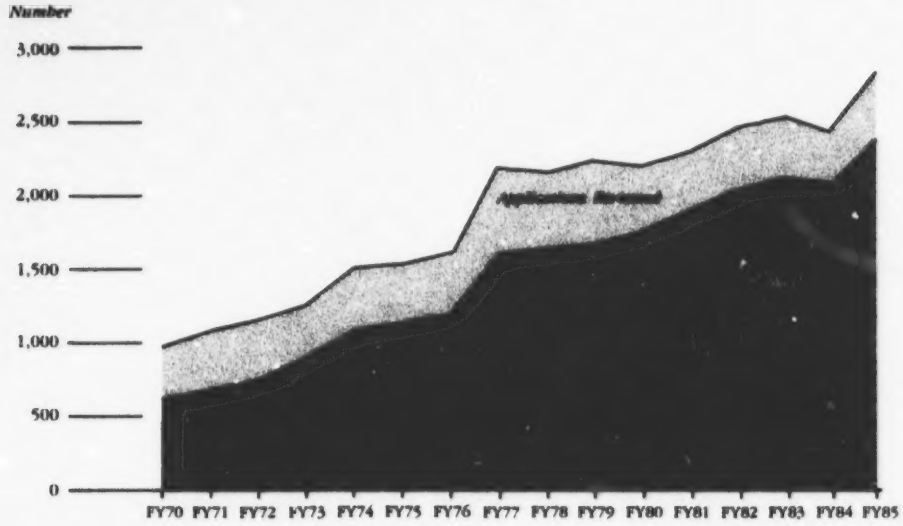
NHLBI Competing Research Project Grants:* Applications Reviewed, Approval Recommended, and Awarded, Fiscal Years 1970-1985



Number of Grants

	FY 1972	FY 1973	FY 1974†	FY 1975	FY 1976	FY 1977	FY 1978	FY 1979	FY 1980	FY 1981	FY 1982	FY 1983	FY 1984	FY 1985
Current Year Applications Reviewed	1,167	1,279	1,501	1,551	1,615	2,180	2,129	2,239	2,190	2,289	2,455	2,519	2,445	2,778
Current Year Approvals Recommended	773	933	1,117	1,137	1,192	1,600	1,595	1,679	1,735	1,890	2,054	2,110	2,115	2,441
Total Eligible‡	777	937	1,155	1,141	1,195	1,602	1,625	1,699	1,741	1,897	2,055	2,114	2,119	2,448
Awarded	492	426	662	629	707	729	759	942	589	774	765	748	852	901
Percent Funded	63%	45%	59%	57%	59%	46%	47%	55%	34%	41%	37%	35%	40%	37%

† Reflects release of fiscal year 1973 impounded funds.

‡ Includes unfunded approvals carried over from previous years which were funded within a specific year.

has increased substantially from fiscal year 1975 to fiscal year 1985, from $327.9 million to $803.8 million. However, as shown in the figure entitled "NHLBI Obligations: Fiscal Years 1975-1985," when the funds are adjusted for inflation (constant dollars), most of the increase disappears ($327.9 million to $408.6 million). With the increasing number of worthwhile applications, many projects that had the potential for leading to improvements in the health of the people of the United States were not funded.

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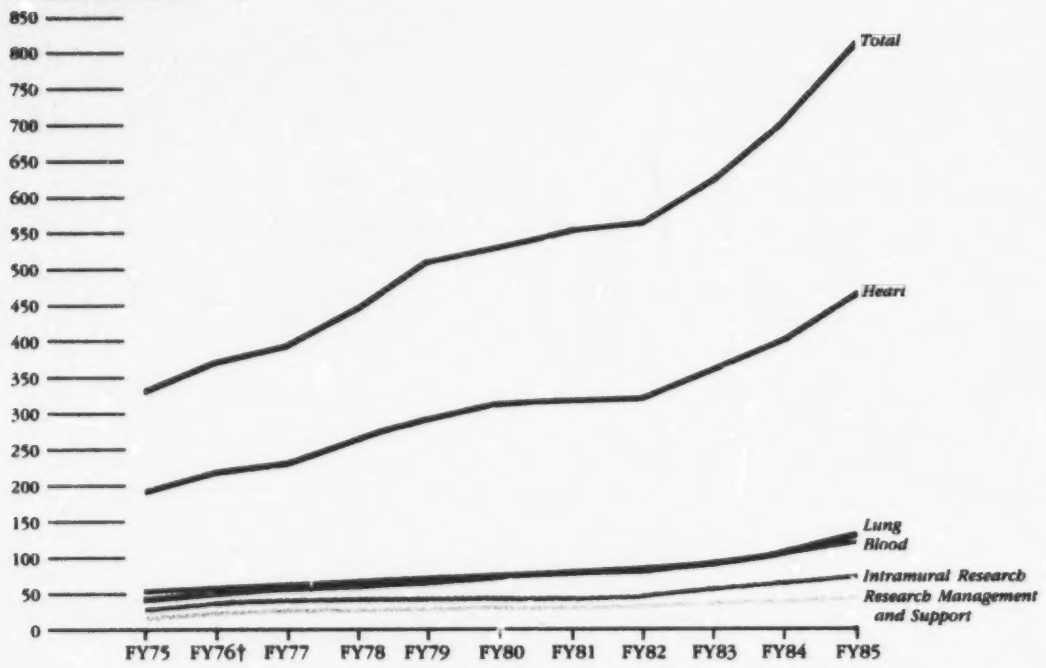
NHLBI Obligations: Fiscal Years 1975-1985

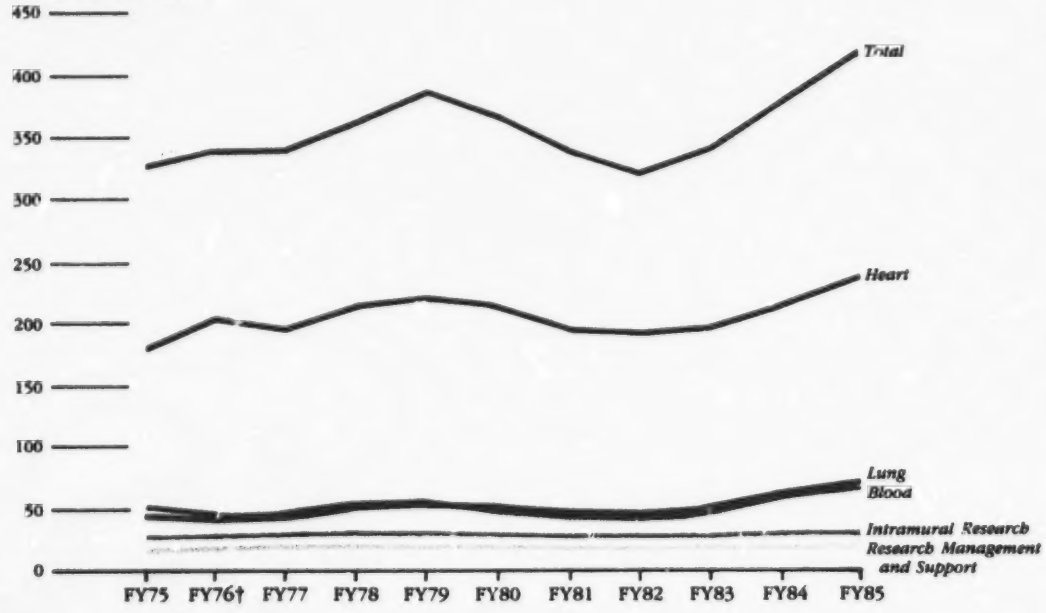
*Current Dollars**

Dollars in Millions



*Constant 1975 Dollars**

Dollars in Millions



** Excludes $3.3 million for Research Facilities Construction Grants in fiscal year 1985.*

† Excludes transition quarter.

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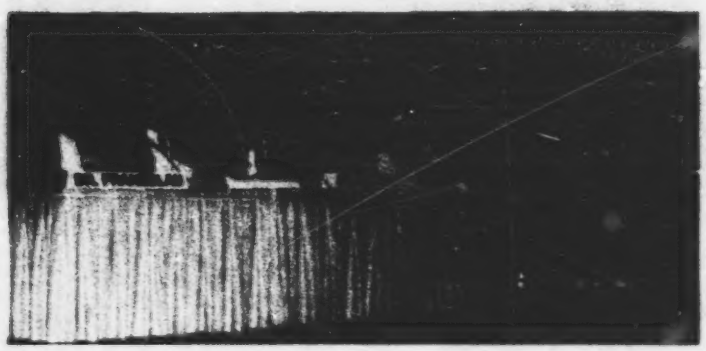
Council Public Briefing Meetings

The National Heart, Lung, and Blood Advisory Council held two public briefing meetings this fiscal year, one on May 3, 1985, in Bethesda, Maryland, and the other on September 30, 1985, in Los Angeles, California. The purpose of these meetings was to give the Council and NHLBI staff an opportunity to hear directly from persons interested in and concerned about the Institute's extramural programs.

Both meetings were well attended. The overriding concern was over the decline in the number of grants compared to the number of applications favorably recommended for funding. More research training support was also felt to be needed. Speakers expressed concern about the number of talented investigators, trained at great expense, who are unable to obtain research funds and are shifting vocations.

Additional themes at the Los Angeles meeting were the need for closer communication between clinical researchers and clinicians; the need for more and larger epidemiologic and disease prevention studies of minority populations; and the need for increased support for research centers, which offer a much needed research resource and provide an environment where both basic and clinical research can flourish.

Council public briefing meeting in Los Angeles.



Clinical Trials

Clinical trials, which are set up in carefully controlled settings, are designed to test the effectiveness and safety of preventive and therapeutic regimens before they are introduced into practice. In this past year, initiatives have been introduced in the areas of prevention of hypertension, treatment of cardiac arrhythmias, the effectiveness of coronary artery bypass grafts, and dietary intervention in children with high LDL (low density lipoprotein) levels.

The Hypertension Prevention Trial will test whether certain dietary regimens can reduce the incidence of definite arterial hypertension. Researchers will study the relationships between obesity, sodium intake, the ratio of sodium to potassium intake, and hypertension. The clinical trial will be conducted in healthy, young-to-early middle-aged adults of both sexes with "high normal" blood pressure. Included will be a substantial proportion of blacks and other individuals with a family history of hypertension.

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The objective of the Cardiac Arrhythmia Treatment Study is to test whether pharmacologic treatment of ventricular arrhythmias occurring after a myocardial infarction can reduce the risk of sudden cardiac death and total mortality. Each year over 400,000 people in the United States die suddenly of coronary artery disease. This full-scale trial will be modeled after the Cardiac Arrhythmia Pilot Study (CAPS), which was completed in 1982. CAPS assessed whether postmyocardial infarction patients with documented ventricular arrhythmia could be identified and enrolled into a double-blind clinical trial, whether good patient compliance could be maintained, and whether one or more drugs could effectively and safely reduce arrhythmia over a 1-year period. The pilot experience demonstrated that patient recruitment is feasible and that good compliance could be achieved. Data on antiarrhythmia drugs are very encouraging. In the Cardiac Arrhythmia Treatment Study, approximately 25 clinical centers will be enrolled involving 4,500 patients over a 3-year period with a subsequent 2 years of followup.

Patients enrolled in the Hypertension Prevention Trial will be placed on certain dietary regimens to determine if the incidence of arterial hypertension can be reduced.

In the Coronary Artery Bypass Graft Clinical Trial, researchers will study patients undergoing coronary artery bypass graft surgery. Objectives will be: to evaluate the effect of multiple lifestyle interventions (smoking cessation, lipid lowering by diet and exercise) and lipid lowering drug interventions on graft patency, progression of coronary atherosclerosis in the distal native vessels, and ventricular function; to identify clinical, biochemical, hemostatic, and operative factors that predict early and late graft narrowing and occlusion; and to identify the behavioral and lifestyle factors contributing to successful adjustment after coronary artery bypass grafts. In 1984, 202,000 patients underwent such grafts in the United States, and such surgery will probably increase.

The role of nutrition and its effect in prevention of disease are important concerns, and so a clinical trial involving dietary intervention in children with high LDL levels will be initiatied to investigate the feasibility, acceptability, efficacy, and safety of such dietary interventions. The dietary regimen for the child and other members of the family at home will be studied. The project will include several collaborating clinical centers, and it is projected that approximately 500 children will be studied over 7 years.

Community Study

The Community Study and Cohort Surveillance Program (CCS)—Field Centers is a key epidemiological study that will be developed to examine atherosclerosis risk in communities. The project will include four geographically distinct field centers, including one with a predominantly black population. A coordinating center, a central hemostasis laboratory, and a central lipid laboratory will also be established. The cohort will contain approximately 4,000 participating men and women, ages 45 to 64 at entry.

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New Programs and Activities

In the recently launched Academic Research Enhancement Award (AREA) program, the NIH has made a special effort to encourage research in educational institutions that provide the baccalaureate training for a significant number of our Nation's research scientists, but which historically have not been participants in NIH programs. This award provides funds for faculty members of those institutions to develop new research projects or expand ongoing research activity in areas related to the Institute's mission.

Two other new or revised awards are the Method to Extend Research in Time (MERIT) and First Independent Research Support and Transition (FIRST) awards. The MERIT award is designed to fund the research on a grant to an outstanding investigator for 5 years, with a possible extension of up to 5 more years after an expedited review process that does not include preparing a new application. This gives the opportunity for experienced and meritorious investigators to spend more of their time doing research rather than reapplying for additional funding.

The FIRST award, which is a modification of the current New Investigator Research Award, is to provide 5 years of research support for newly independent biomedical investigators. This will allow such investigators sufficient time to develop their research capabilities and to demonstrate the merit of their research ideas.

With respect to the Small Business Innovation Research (SBIR) program, which was discussed in last year's report, the Council is pleased to note that the quality of the SBIR applications has shown a marked improvement this year. The SBIR program has become an integral and a well-justified part of the overall NHLBI extramural program.

Minority Activities

The NHLBI is continually developing and evaluating programs for and projects about minorities, as evidenced by a special report that was published in 1986. This report provides a detailed inventory of past and present Institute-sponsored research and other activities dealing with blacks and other minorities. Some of the many projects and programs include: 1) a study on biobehavioral factors affecting hypertension in blacks; 2) a study of diabetes and cardiovascular risk factors in Mexican Americans; 3) longitudinal studies of coronary heart disease risk factors in young adults (one-half of whom are black); 4) a community surveillance system for cardiovascular and other chronic diseases (both blacks and whites); 5) the Honolulu Heart Program, which will compare mortality rates and trends in coronary heart disease in men of Japanese ancestry living in Honolulu with men of Japanese ancestry in San Francisco and Japan; 6) the Minority Summer Program in Pulmonary Research, which provides promising minority students an opportunity to receive summer training in the laboratories of established pulmonary investigators; 7) sickle cell disease projects; and 8) the Minority Faculty Development Award, whose goal is to encourage the development of minority investigators in areas relevant to cardiovascular, pulmonary, or blood diseases. Candidates for this last award will be faculty members at minority institutions, who will be supported for 5 years to do intensive research.

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Budget Recommendations

The National Heart, Lung, and Blood Advisory Council is firmly committed to a balanced and diverse program of biomedical research and training for the benefit of the public health. Such a program makes use of a variety of support mechanisms, including investigator-initiated research project grants as well as program project grants, institute-initiated research and center grants, and contracts. The program includes basic as well as applied and clinical research, laboratory and clinical trials, and demonstration and education activities.

In recommending budgets for FY 1988 through FY 1992, the Council reaffirms these principles for the determination of funding levels:

- Budgets must increase to keep pace with increasing costs of doing research.
- A reasonable percentage of uncommitted funds each year must be used for centers, contracts, training, career awards, and other research mechanisms that make up a balanced Institute program, while adequate funds are also provided for research project and program project grants.
- Resources must be sufficient to fund as many approved applications for research grants as possible.
- Administrative flexibility must be provided to NHLBI to allow effective deployment of its allocated resources.

The Council believes that the current level of funding impedes the efforts of the Institute to award an adequate number of promising research projects in all areas and to develop fully its initiatives in such priority areas as clinical trials and the career development of newly trained and minority scientists. Therefore, the Council strongly recommends the following budget:

FY 1988	FY 1989	FY 1990	FY 1991	FY 1992
1,062.2M	1,115.3M	1,171.1M	1,229.6M	1,291.1M

While these figures represent a substantial increase from present expenditures, the funds are still extremely modest when seen in perspective. For example, in 1984, Americans spent approximately $28.8 billion on cigarettes and $35.7 billion on beer. Surely, $1.06 billion in FY 1988 is not too much to spend for research into the treatment, cure, and prevention of diseases of the heart, lungs, and blood, which include the leading cause of death (heart disease) as well as the third (cerebrovascular diseases), fifth (chronic obstructive pulmonary disease), and tenth (atherosclerosis) leading causes of death in the United States today.

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Conclusion

In conclusion, the National Heart, Lung, and Blood Advisory Council wants to commend the Director, Dr. Claude Lenfant, and the entire staff of the NHLBI for the high quality work they do. These dedicated people work far beyond the customary hours. Their commitment to the Council, to those involved in biomedical research in this country, and to the general public, all of whom they serve, is exemplary. Because of a restrictive budget and rising costs, the number of NHLBI staff has decreased substantially, a situation that has put extra burdens on those remaining. Also, the Council is concerned with the number of truly outstanding applications from gifted research investigators, especially new investigators, that have not been awarded because the budget is so severely restricted. These investigators are the future of health science in our country. They should not be discouraged, for their efforts lead to improved health and prevention of disease, which are the legacies we all wish to leave our children and grandchildren. The Council is strongly committed to doing everything possible to see that these legacies become reality.

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